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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/877,220	06/08/2001	Karin Westlund High	265.0019 0101	8535

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EXAMINER	
BRANNOCK, MICHAEL T	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 05/18/2004

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/877,220	HIGH ET AL.	
	Examiner	Art Unit	
	Michael Brannock	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 April 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20,21,24 and 29-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *20, 21, 24, 29-33,36-45,48-53 and 56-67* is/are rejected.

7)☒ Claim(s) *34,35,46,47,54 and 55* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 April 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application: Claims and Amendments

Applicant is notified that the amendments put forth on 4/29/03, have been entered in full.

Response to Amendment

Applicant is notified that any outstanding objection or rejection that is not expressly maintained in this Office action has been withdrawn in view of Applicant's amendments and persausive arguments.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 20, 21, 29, 32, 33, 36, 37, 42-45, 60 and 61 are rejected under 35 U.S.C. 102(b) as being anticipated by Rao et al., Neuron, 19(801-812)1997.

Rao et al., disclose an assay that monitors NR1 subcellular distribution, comprising contacting a neuron with an amount of a compound effective to alter the subcellular distribution of NR1, e.g. APV or Tetrodotoxin (TTX), and activating an NMDA receptor (e.g. by culturing the cells under conditions which allow spontaneous activation of the receptor (as when testing APV) or by adding NMDA (as when testing TTX), see col 1, page 804), and detecting the distribution of NR1 in a neuron, e.g. see Figure 3 and the amount of NR1 in a neuron (see col 1 of page 803 and col 2 of page 805).

Applicant correctly points-out that the prior Office action wrongly asserted that it was APV not TTX that was used in conjuction with NMDA in the method taught by Rao et al. With this in mind, Applicant arguments will be addressed as they may relate to the corrected rejection. Applicant argues that culturing the cells with both TTX and NMDA "largely blocked the increase in NR1 cluster number and a shift to synaptic sites induced by TTX"; thus, Applicant, presumbly, argues that the distribution of NR1 subunit in the cell contacted with the compound was not altered. This argument has been fully considered but not deemed persuasive for two reasons. First, the distribution of the NR1 subunit was altered by the presence of the TTX, see Figure 3, wherein the number of NR1 clusters is greater in both TTX treatments compared to the controls. Second, and more importantly regarding claims 20 and 21, the claims claim a method for identifying a compound that alters NR1 subunit distribution, the method of Rao et al., would certainly accomplish this regardless of whether or not the compound used actually produced the effect. This concept holds true for claim 21 as well, because Rao et al. clearly indicate that any change in amount would be measured, see col 1 of page 803; thus the general method, as claimed, is taught by Rao et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 24, 38, 39, 48, 49, 52, 53, 56, 57, 66, and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rao et al,., Neuron, 19(801-812)1997 in view of Wang, YT et al., PNAS 93(1721-1725)1996 .

Rao et al., disclose an assay that monitors NR1 subcellular distribution, comprising contacting a neuron with an amount of a compound effective to alter the subcellular distribution of NR1, e.g. APV or Tetrodotoxin (TTX), and activating an NMDA receptor (e.g. by culturing the cells under conditions which allow spontaneous activation of the receptor (as when testing APV) or by adding NMDA (as when testing TTX), see col 1, page 804), and detecting the distribution of NR1 in a neuron, e.g. see Figure 3 and the amount of NR1 in a neuron (see col 1 of page 803 and col 2 of page 805). The central finding of Rao et al. is that it is the activity of the NMDA receptor that regulates its subsellular distribution (see the Title); Rao et al. specutlate that phosphorylation may be involved in this regulation but do not specifically mention tyrosine phosphorylation. Wang, YT et al. teach that tyrosine phosphorylation regulates NMDA receptor activity, and use tyrosine kinase inhibitors and tyrosine phosphatase inhibitors to modulate the activity of NMDA receptors (see the Abstract).

Therefore, one of ordinary skill in the art, at the time the invention was made, and with reasonable expectation of success, would be motivated to assay tyrosine kinase inhibitors and tyrosine phosphatase inhibitors as taught by Wang in the method of Rao, the motivation to do so is provided by Rao who teach that activity regulates the subcellular distribution of NMDA receptors and by Wang who teach that tyrosine phosphorylation modulates activity.

Claims 38-41, 48-51, 58, 59, 64, 66 and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rao et al,., Neuron, 19(801-812)1997 in view of Ehlers, MD et al., Science 269(1734-1737)1995.

Rao et al., disclose an assay that monitors NR1 subcellular distribution, comprising contacting a neuron with an amount of a compound effective to alter the subcellular distribution of NR1, e.g. APV or Tetrodotoxin (TTX), and activating an NMDA receptor (e.g. by culturing the cells under conditions which allow spontaneous activation of the receptor (as when testing APV) or by adding NMDA (as when testing TTX), see col 1, page 804), and detecting the distribution of NR1 in a neuron, e.g. see Figure 3 and the amount of NR1 in a neuron (see col 1 of page 803 and col 2 of page 805). The central finding of Rao et al. is that it is the activity of the NMDA receptor that regulates its subsellular distribution (see the Title); Rao et al. specutlate that phosphorylation may be involved in this regulation but do not specifically mention phosphorylation of the NR1. Ehlers teach that serine phosphorlyation of NR1 regulates subcellular distribution of the NMDA receptor, see the Abstract and col 1 of page 1736.

Therefore, one of ordinary skill in the art, at the time the invention was made, and with reasonable expectation of success, would be motivated to assay serine/threonine phosphatase inhibitors and to measure NR1 phosphorylation as taught by Ehlers when practicing the method of Rao, the motivation to do so is provided by Rao who teach that activity regulates the subcellular distribution of NMDA receptors and by Ehlers who teach that such alterations in subcellular distribution are accompanied by changes in NR1 phosphorylation.

It is noted that Ehlers did not appear to find nuclear translocation of the NR1 subunit, which would appear to be in contradiction to the instant application, however, this may be

explained by the absence of NMDA receptor single transduction mechanisms present in the cell type used by Ehlers and/or by the lack of NMDA receptor activitity. It is also noted that the instant specification indicates that changes in NR1 phosphophorylation accompany changes in receptor tyrosine kinase activity, however there is no teaching that NR1 is phosphorylated on tyrosine (see page 29), and it is assumed that the anti-phospho-NR1 antibody refered to on page 29 recognizes a phosphorylated serine or threonine.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29-31, and 60-67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of altering the NR1 subunit distribution in a cell, wherein the alteration in tha total amount of NR1 subunit in the cell increases or decreases, and the nuclear translocation of NR1 is altered, comprising contacting a cell with a tyrosine kinase inhibitor or tyrosine phosphatase inhibitor, does not reasonably provide enablement the above such alterations comprising contacting the cell with any other type of compound . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The specification discloses experiments where in tyrosine kinase inhibitors are used to inhibit the NMDA-receptor-activity dependent translocation of the NR1 subunit to the nucleous; this inhibition is also accompanied by an inhibition of the NMDA-receptor-activity dependent

increace in the total amount of NR1 subunit, see Examples I and II. Claims 31 and 63 specifically require the opposite effect, i.e. that the prescence of the compound increase the total amount of NR1 in the cell. No such compounds were demonstrated to do this, however, it is generally assumed that effects opposite of tyrosine kinase inhibitors can be achieved using tyrosine phosphatase inhibitors, as examplified by Wang, YT et al., PNAS 93(1721-1725)1996, see the Abstract.

The instant claims, however, encompass any and all compounds that may one day prove to have this effect, yet are not disclosed in the specification. And one of ordinary skill in the art would not expect that all or most compounds could alter the subcellular distribution of the NR1 subunit, and of those that could, Rao et al,., Neuron, 19(801-812)1997 teach that one could not expect that the total amount of the NR1 subunit or its nuclear translocation would be altered, see the first paragraph of page 803. The instant claims to the use of this large genera is not supported by a commensurate teaching as to which compounds could actually be used The claims are, in essence, single means claims, because the claims encompass any composition having the recited activities whereas the instant specification only discloses those two types of compositions known to the inventor, i.e. tyrosine kinsase inhibitors and tyrosine phosphatase inhibitors. In *In re Hyatt*, 708 F.2d 712, 218 USPQ 195 (Fed. Cir. 1983), a single means claim which covered every conceivable means for achieving the stated purpose was held nonenabling for the scope of the claim because the specification at most disclosed only those means known to the inventors. When claims depend on a recited property, a fact situation comparable to *Hyatt* is possible, where the claim covers every conceivable structure (means) for achieving the stated

property (result) while the specification discloses at most only those known to the inventor. See also *Fiers v. Sugano*, 984 F.2d 164, 25 USPQ2d 1601 (Fed. Cir. 1993), and MPEP § 2164.08(a).

Thus, the specification has simply offered an invitation to begin a trial and error course of experimentation to try to find other such compounds, if they can be found, to try to find compounds that could be used commensurate with that which is claimed. Such random trial and error experimentation is unduly burdensome.

Claims 29, 30, 31and 60-67 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification dicloses that tyrosine kinsase inhibitors and tyrosine phosphatase inhibitors can alter the nuclear localization and total amount of NR1 in a cell yet the claims encompass the use of any compounds, yet to be discovered that could accomplish this. Although one of skill in the art would reasonably predict that these compounds exist or could exist, one would not be able make useful predictions as to the nucleotide positions or identities of those sequences based on the information disclosed in the specification.

The instant disclosure of compounds having a single mode of action, i.e. modulating tyrosine phosphorylation, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). A description of a genus

of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification discloses, however, only two polynucleotide sequences, which is not sufficient to describe the essentially limitless genera encompassed by the claims.

With the exception of tyrosine kinsase inhibitors and tyrosine phosphatase inhibitors referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed compounds and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only tyrosine kinsase inhibitors and tyrosine phosphatase inhibitors, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Allowable Subject Matter

Claims 34, 35, 46, 47, 54, 55 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (571) 272-0869. The examiner can normally be reached on Mondays through Fridays from 10:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, Ph.D., can be reached at (571) 272-0887.

Official papers filed by fax should be directed to (703) 872-9306. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

MB

ELIZABETH KEMMERER
PRIMARY EXAMINER

May 16, 2004